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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/315,673 09/30/94 CASKEY

C D5050CCC

EXAMINER
MARSCHEL, A

18N1/0404

ART UNIT PAPER NUMBER

34

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1807

DATE MAILED: 04/04/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9-30-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
Of the above, claims 9-17 are withdrawn from consideration.
2. ☐ Claims have been cancelled.
3. ☐ Claims are allowed.
4. ☒ Claims 1-8 and 18-24 are rejected.
5. ☐ Claims are objected to.
6. ☒ Claims 1-24 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____ Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicants' amendments, filed 9/30/94, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

During a telephone conversation with Thomas Paul on 1/4/90 in parent application serial number 07/256,689; a provisional election was made with traverse to prosecute the invention of Group I, claims 1-8 (now claims 1-8 and 18-24). Since the instant application is the latest file-wrapper-continuation in a series of FWCs from 07/256,689; this election is assumed to be carried forward to the instant application. Affirmation of this election without traversal arguments was made by applicants in Paper No. 7, filed 8/6/90. Claims 9-17 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The amendment, filed 9/15/92, is objected to under 35 U.S.C.

§ 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The bottom 7 lines of the amended Table 1 which cite publications and other explanations regarding melting temperature contain NEW MATTER because these disclosures detailing T_m calculation methods have no written basis in the disclosure as filed. It is acknowledged that T_m values under standard conditions such as 1M monovalent cation concentration are inherent given the primer sequences. The Examiner regrets the delay in noting this NEW MATTER since this amended Table 1 was filed 9/15/92.

Applicant is required to cancel the new matter in the response to this Office action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

The limitation of claim 18 to a T_m spread of no more than 8.5 degrees C is NEW MATTER. The specific melt temperatures given in Table 1 are just that, specific melt temperatures.

There is no disclosure in the instant application, as filed, that a "range" of T_m values for primers used in multiplex PCR such as T_m values varying no more than 8.5 degrees C is a limitation of the instant invention. It is also noted that the specification on page 3, lines 16-36, discusses the falling apart of PCR when primers for more than two sequences are added, but that the instant disclosure as filed never discloses that limiting the T_m range of primers used together is a solution for this nor even contemplated by the inventors as part of the solution. Similar to the above NEW MATTER, the 4.5 degree C limitation of claim 19 is a range not supported by specific melt temperature disclosures. It is additionally noted that the maximum T_m spread in Table 1 is 8.3° C, not 8.5 degrees, and clearly not 4.5 degrees. Again supporting the lack of written description for these temperature range limitations. Claims 21-24 also contain these NEW MATTER T_m ranges.

Claims 18, 19, and 21-24 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 21-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The last 2 or 3 lines of claims 21-24 are vague and indefinite because there is no citation that relates back to the preamble detection practice of the claims. That is, all of the

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claims cite the formation of amplification product as a positive and necessary result of the claimed method. This does not take into account the intent cited in the preamble to detect deletions or sequences. Thus the claims do not include the non-detection of amplified product as being indicative of the absence of target from a starting DNA sample. Clarification of whether the claimed method is intended to only be a method of amplification or whether detection inclusive of the absence or presence of target nucleic acids is being claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8 and 18-24 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Chamberlain et al. (1988 Am J. of Human Gen. Vol. 43, Abstract 0711).

The content of abstract 0711 indicates the instant invention was known or used by others due to the difference between the instant inventorship as compared to the authorship of this abstract. N. J. Farwell is listed as an author but not as an instant inventor.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-3, 7, and 18-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Kogan et al.

The instant invention is directed to the practice of PCR wherein three or more primer pairs are simultaneously used in one reaction mixture to amplify respectively three or more different target sequences.

Kogan et al. disclose the use of two primer pairs in PCR as depicted in Figures 1 and 2. It is noted that the primer pairs that were amplified together in Figure 2 were different from those used for Figure 1 to obtain a clearer result. It is noted, however, that both sets of primer pairs gave usable results thus suggesting that the primer pairs may be interchanged as desired

Applicants have also argued in the past that the primer pairs of the invention must have T_m values within a certain range. It is noted that the primers, except for one primer, disclosed by Kogan et al. are of similar length and percent GC content and are expected therefore to also have T_m values that are relatively close to each other. The one primer that contains a string of G residues would be expected to have a distinctly higher T_m value than the other primers. Since this primer also functions well in the Kogan et al. assays, there is therein evidence that multiplex PCR does not require that primers used together must have T_m values that fall within a relatively small range contrary to the assertion of applicants. Thus, the asserted problem of applicants regarding the use of more than two primer pairs does not seem to be recognized in the art as a problem to be overcome. Rather multiplex PCR appears to function well as long as the reaction temperature during PCR is significantly below the lowest T_m of those primers used together. Additionally, applicants have asserted that this T_m range limitation unexpectedly overcomes the problems of multiplex PCR with more than two primers. Consideration of the prosecution history of this application and its parents reveals that this is an assertion with results as evidence to support it as a solution to a problem. That is, applicants have not set forth any unexpected results that multiplex PCR is non-functional when primers are used together with widely varying T_m values wherein by comparison primers used together wherein a small range of T_m

with some change in result quality but yet functional in both cases. Kogan et al. does not recognize any problem with multiple primer usage as suggested in the instant specification. In fact Kogan et al. disclose a suggestion and motivation to use multiple primer pairs in PCR without limitation to only two primer pairs in the discussion on page 990, first column, lines 24-27.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice multiple primer pair usage in PCR such as three pairs or more because Kogan et al. disclose results from two primer pair usage as very clear and readable results and suggest multiple pair usage without limiting such usage to two primer pairs as noted above giving a reasonable expectation of success for such multiplex PCR practice with three or more primer pairs as instantly claimed.

It is also noted that applicants previously attempted to overcome this rejection with a Declaration under 37 CFR § 1.131 but that reconsideration of this Declaration reveals two insufficiencies. One insufficiency is that only one of the instant inventors signed said Declaration whereas in contrast such Declarations must be made by all of the inventors. The second insufficiency is that there is no statement therein that the invention was conceived and/or reduced to practice in the United States. It is noted that Ann Arbor, Michigan is mentioned in the Declaration but not that this was the location of the conception and/or reduction to practice of the instant invention.

values as claimed give improved or functional results. This lack of unexpected results fails to support the assertions of applicants. Assertions without factual evidence are deemed non-persuasive in overcoming a rejection in such cases as this.

Additionally, the above rejection includes those claims cited above as containing NEW MATTER in anticipation of removal of said NEW MATTER thus leaving the subject matter of the claims properly rejected as summarized above.

Claims 1-8 and 18-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Kogan et al. taken in view of Koenig et al. (1987) or Koenig et al. (1988).

The basic instant invention is summarized in the above rejection. The embodiments hereinunder rejected are those directed to the multiplex amplification and detection of various X-linked muscular dystrophy targets corresponding to segments mutated in abnormal individuals in the dystrophin gene.

Kogan et al. has been summarized above as suggesting the basic invention. Kogan et al. disclose the motivation and suggestion for multiplex PCR as being useful in a variety of disorders caused by gene deletions on page 990, first column, lines 27-32. Kogan et al., however, lacks disclosure of mutations corresponding to X-linked muscular dystrophy in the dystrophin gene.

Either Koenig et al. reference disclose the cDNA and various aspects of the genomic organization of the dystrophin gene as they are related to disorders in X-linked muscular dystrophy.

These disclosures supply the sequence information and locations of important mutations that motivate and suggest regions that should be amplified as important in muscular dystrophy assays.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the dystrophin gene amplification practice in multiplex PCR with detection of amplification products for diagnosis because Kogan et al. disclose the basics of multiplex PCR as doable and suggest its use in other disorders amenable to PCR analysis and the Koenig et al. references cite the sequences and loci of interest in X-linked muscular dystrophy diagnosis.

Applicants are reminded that perfection of the previous Declaration under 37 CFR § 1.131 would overcome the art rejections herein set forth.

Prior art made of record in the parent applications serial numbers 07/256,689; 07/770,742; and 08/060,463; is hereby also made of official record as having been considered in the instant application.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is either (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr, can be reached on (703) 308-2454.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM A. MARSCHEL:am

March 31, 1995

SW Zitomer
STEPHANIE W. ZITOMER
PRIMARY EXAMINER
GROUP 1800